Concurrently with this communication, Applicants are filing a Request for Continued Examination and an Information Disclosure Statement. Withdrawal of the finality of the previous rejection and continuation of prosecution is requested.

REMARKS

I. Telephonic Interview

Applicants wish to thank the Examiner for the courtesy of the telephonic interview of February 12, 2003.

II. Claim Rejection – 35 U.S.C. §103(a)

The rejection of claims 1, 3-20 and 23-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Makino et al. (EP 0237 200) ("Makino") has been maintained.

The Examiner alleges that Makino contemplates both sustained-release and enteric-coated oral formulations of a benzimidazole compound. According to the Examiner, a person of ordinary skill in the art would have been guided by Makino to select those coating agents that provide sustained release properties, e.g., a water-insoluble polymer such as ethyl cellulose. The Examiner states that the Examples and claim 9 of Makino, which are directed to an enteric-coated formulation, are representative of the best mode. However, the Examiner contends that the prior art effect of Makino is not limited to the Examples and claim 9. Therefore, the Examiner concludes that it would have been obvious to apply the teachings of Makino to formulate a sustained-release formulation of omeprazole comprising an ethyl cellulose coating.

The claimed dosage form is not enteric coated. Rather, the core material is coated with a disruptable, semi-permeable membrane consisting essentially of a water-insoluble polymer and a

modifying agent to produce a delayed release of the active ingredient. The core material comprises omeprazole, an alkaline salt thereof, S-omeprazole or an alkaline salt thereof (hereinafter collectively referred to as "omeprazole"). The omeprazole core includes one or more alkaline additives, one or more swelling agents and, optionally, pharmaceutically acceptable excipients.

The prior art effect of Makino must be interpreted as of its priority date and not with the benefit of hindsight. The earliest priority date of Makino is February 13, 1986. Applicants submit that the overwhelming weight of evidence supports the position that Makino, in 1986, did not contemplate or suggest an oral formulation of omeprazole without an enteric coating. Accordingly, Makino was not in any position to offer guidance, as alleged by the Examiner, to produce a delayed release oral formulation of omeprazole with a disruptable semipermeable membrane to provide delayed release properties, and that is not enteric coated.

As discussed below, it was the art-recognized practice in 1986 to apply an enteric coating layer to oral dosage forms of omeprazole to protect the acid-labile substance omeprazole from degradation and transformation in acidic to neutral media. In 1986, the person of ordinary skill in the art knew that an enteric coating layer was necessary to ensure that the active ingredient was protected and transferred in an intact form to that part of the gastrointestinal tract where the pH is near neutral and where rapid absorption can occur. Furthermore, Applicants submit that the same understanding regarding enteric coated formulations of omeprazole which prevailed in 1986 continued to prevail as of June 22, 1999, i.e., the priority date of the subject application.

Attached to this communication is an Information Disclosure Statement ("IDS") citing four documents which Applicants are submitting in support of their position that Makino, in 1986, did not contemplate or suggest an oral formulation of omeprazole without an enteric

coating. These documents are representative of the prior art relating to oral formulations of omeprazole. A copy of each of the documents listed on the Form PTO-1449 attached to the IDS is also enclosed. For the Examiner's convenience, a summary of the relevant documents is set forth below.

1. EP 0 124 495

EP 0 124 495 ("EP '495") is directed to alkaline salts of omeprazole. The priority date of EP '495 is March 4, 1983. With respect to the preparation of pharmaceutical formulations, EP '495 discloses that granules or tablets are preferably layered with an enteric coating which protects the active compound from degradation while the dosage form remains in the stomach (p. 6, lines 24-28). Example 12 is the only example relating to a solid oral dosage form. In Example 12, the tablet containing omeprazole magnesium salt is enteric coated.

Therefore, as early as 1983, it was known in the art that omeprazole, without the protection of an enteric coating layer, was subject to degradation while the dosage form remained in the stomach. Applicants submit that this is a teaching against the making and use of an oral dosage form of omeprazole that is not enteric coated.

2. Pilbrant, Å, et al., Development of an oral formulation of omeprazole, Scandinavian Journal of Gastroenterology, 20 (suppl 108):113-120 (1985)

Page 113 of the Pilbrant et al. publication provides that preformulation studies showed that moisture, solvents and acidic substances had a deleterious effect on the stability of omeprazole and should be avoided in pharmaceutical formulations. Pages 114-115 indicate that an oral dosage form of omeprazole having no enteric coating was determined to be infeasible as

a dosage form having any pharmacological benefit. It was shown that more than half of the omeprazole degraded in the stomach. It is reported that an enteric-coated dosage form of omeprazole offered the best possibility.

Applicants submit that the Pilbrant et al. publication reinforces the teachings of EP '495.

3. EP 0 247 983

EP 0 247 983 ("EP '983") is directed to an oral dosage form comprising omeprazole as the active ingredient. The priority date of EP '983 is April 30, 1986, i.e., less than two months after the priority date of Makino. On page 1 of the background section of EP '983, it is disclosed that

> ...it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation. (page 1, lines 29-32)

Furthermore, on page 2 it is disclosed that

> In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores ***must be enteric coated***. (page 2, lines 7-9) (Emphasis added)

Therefore, even at the time Makino was filed, it was still accepted pharmaceutical practice to coat oral dosage forms of omeprazole with an enteric coating layer. There is no hint of recognition of an oral dosage form of omeprazole that is not enteric coated. Thus, in view of the recognition in the art that an enteric coating was required to protect omeprazole from degradation in the stomach, Applicants submit that Makino could not, as of 1986, offer any guidance to formulate an oral solid dosage form of omeprazole that is not enteric coated but instead has a semipermeable membrane that is able to disrupt to provide delayed release properties.

4. WO 98/00114

Although subsequent to the 1986 priority date of Makino, an English language translation of WO 98/00114, published January 8, 1998, is included to show that the application of an enteric coating layer remained the accepted practice in formulating oral dosage forms of omeprazole.

In view of the foregoing, Applicants submit that Makino, when considered as of its 1986 priority date and not with the benefit of hindsight, did not contemplate or suggest an oral formulation of omeprazole without an enteric coating. Moreover, as supported by WO 98/00114, it was indeed unexpected at the time the claimed invention was made that an oral dosage form comprising omeprazole could be prepared without an enteric coating.

Furthermore, there is no recognition by Makino that the claimed dosage form, by virtue of the disruptable, semipermeable membrane, would provide a ***delayed release*** of the active ingredient. As demonstrated by Example 4 of the application, the onset or start of dissolution after two hours of pre-exposure in acid medium is delayed, and almost 3 hours are required to obtain a release of at least 73% of the active ingredient from dosage forms prepared in accordance with the claimed invention:

TIME (hours) (after 2 hours of pre-exposure in acid medium)	% release of active ingredient
0.5	3
1	18
2	60
3	73

In contrast, Makino states that dosage forms may be coated with a water-soluble or water-insoluble polymer by a per se known method for the purpose of masking the taste or providing the dosage forms with enteric or ***sustained release*** property (page, 8, lines 36-37). Applicants submit that the pharmacological characteristics of a sustained release formulation is distinguishable from the ***delayed release*** of the claimed dosage form. A sustained release is a type of controlled release that provides a dissolution of the active ingredient over a sustained or extended period of time. However, such a sustained release is not characterized by the delayed or extended onset or start of dissolution which is observed with the claimed dosage form having a disruptable, semipermeable membrane according to the claimed invention and as shown by Example 4.

On pages 2-3 of the Office Action, the Examiner relies on Example 8 of Makino for the alleged disclosure of sucrose and corn starch as modifying agents. However, these so-called modifying agents are not part of a membrane. In the present invention, the modifying agents are an essential part of a membrane with disrupting properties to provide a delayed release of the active ingredient from the dosage form (See claim 1). Applicants submit, therefore, that Example 8 does not disclose or suggest a dosage form coated with a semipermeable membrane that is able to disrupt. In fact, the only coating disclosed by Makino is the enteric-coated formulation of Examples 7 and 9.

When viewed in its entirety, the disclosure of Makino is directed to the preparation of enteric dosage forms of omeprazole which, at the time the claimed invention was made, were validated and widely accepted by the -pharmaceutical industry. The cited prior art offers no suggestion of using a disruptable, semipermeable membrane comprising a water-insoluble polymer and a modifying agent to prepare an enteric-coatingless dosage form of omeprazole.

Accordingly, the Examiner's analysis of Makino constitutes an improper hindsight reconstruction of the claimed invention.

In summary:

- the prior art effect of Makino must be interpreted as of its priority date (February 13, 1986) and not with the benefit of hindsight;
- the prior art in 1985 (Pilbrant et al.) provided that an oral dosage form of omeprazole having no enteric coating was infeasible as a dosage form having any pharmacological benefit;
- the prior art in 1986 (EP '983) provided that an enteric coating layer was necessary to ensure that the active ingredient was protected and transferred in an intact form to that part of the gastrointestinal tract where the pH is near neutral and where rapid absorption can occur;
- the only examples of a coated oral formulation of omeprazole provided by the prior art, including Makino, during the period 1986-1998 are enteric-coated formulations; and
- there is no recognition by Makino that the presently claimed dosage form, by virtue of a disruptable, semipermeable membrane, would provide a ***delayed release*** of the active ingredient.

For all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness. Withdrawal of the rejection based on Makino is requested.

CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. It is respectfully submitted that claims 1, 3-20 and 23-27 are in condition for allowance, which action is earnestly solicited.

Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: Feb. 27, 2003

Respectfully submitted,

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